which discloses detection of mitochondrial mutations that "were mostly homoplasmic." (Page 7, line 31.) Claims 2, 29, and 31 have each been amended to recite "substitution" in place of "mutation" to refer properly to claim 1 as amended.

New claim 33 recites that the substitution of claim 1 is "a T to a C mutation" and new claim 34 recites that the substitution is "a G to an A mutation." New claims 33 and 34 are supported by the specification which discloses that "any single basepair substitution is conceivable within the scope of the invention, the most frequently encountered substitution are those which are consistent with oxidative damage, such as T to C or G to A transitions." (Page 3, lines 16-18.)

New claim 35 recites a method similar to originally filed claim 1 but for the recitation "wherein the mutation has previously been identified as a somatic mutation in a tumor." Thus new claim 35 is supported by originally filed claim 1 and the specification which discloses, "The method can also be carried out subsequent to the discovery of a somatic mutation in a mitochondrial genome of a cell of the patient or of another patient. In this case, a previous association of the somatic mutation with the presence of a tumor in the patient or in another patient strongly indicates the presence of tumor cells in the patient" (Page 6, lines 16-21.)

New claims 36-53 depend from claim 35. These claims are similar to and supported by originally filed claims 3-16 and 29-32.

None of these amendments introduce new matter.

The Rejection of Claims 1, 9, 10, 29, 31, and 32 Under 35 U.S.C. § 102(b)

Claims 1, 9, 10, 29, 31, and 32 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alonso *et al.* (*Electrophoresis*, 1997, *18*, 682-685; "Alonso"). Applicants respectfully traverse.

Claim 1 is the only independent claim of the rejected claim set. Claims 9, 10, 29, 31, and 32 are dependent on claim 1. Claim 1 is directed to a method to aid in detecting the presence of tumor cells in a patient. The presence of a homoplasmic single basepair substitution is determined in a mitochondrial genome of a cell sample of a patient but not in normal tissue of the patient. The patient is identified as having a tumor if one or more single basepair substitutions are determined in the mitochondrial genome of the cell sample of the patient.

To reject a claim as anticipated, each element of the claim must be found in a single prior art reference. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Alonso screened for somatic mutations in the control region of mitochondrial DNA (mtDNA) in colorectal and gastric tumor cells. (Page 682, column 2, lines 11-13.) Alonso did not, however, determine a "homoplasmic single basepair substitution" as recited in amended claim 1. The mutations identified by Alonso included:

> [A] heteroplasmic A:T/G:C transition [that] was detected in the HV1 [hypervariable 1] region at nucleotide position 16241 and 16166, respectively . . . a heteroplasmic C:G/T:A transition at position 312 in patient 6, a homoplasmic 1-base-pair C:G deletion at position 309, a heteroplasmic A:T/G:C transition at position 93 and a 2-

> base-pair CC:GG insertion at position 309 in patient 14, and a heteroplasmic C:G/T:A transition in patient 19 at position 76.

Page 684, column 2, line 6 to page 685, column 1, line 8. None of the mutations determined by Alonso is a homoplasmic substitution mutation as required by claim 1. Thus Alonso does not expressly or inherently teach each and every element of claim 1. Because claims 9, 10, 29, 31, and 32 depend from claim 1 they also require this element. Thus Alonso anticipates none of claims 1, 9, 10, 29, 31, and 32.

Withdrawal of this rejection to claims 1, 9, 10, 29, 31, and 32 is respectfully requested.

Alonso also does not anticipate new claims 35-53. Claim 35 is the only independent claim of the new claim set. Claim 35 is directed to a method to aid in detecting the presence of tumor cells in a patient. The presence of a single basepair mutation is determined in a mitochondrial genome of a cell sample of a patient. The mutation is found in a tumor of the patient but not in normal tissue of the patient. The mutation has previously been identified as a somatic mutation in a tumor. The patient is identified as having a tumor if one or more single base pair mutations are determined in the mitochondrial genome of the cell sample of the patient.

Alonso also does not anticipate these claims because Alonso does not expressly or inherently teach detection of a single basepair mutation in a mitochondrial genome "wherein the mutation has previously been identified as a somatic mutation in a tumor." Alonso, rather, determined <u>if</u> mtDNA mutations were present in tumor cells. "The aim of this study was to evaluate if this intrinsic [genetic] instability displayed by the mtDNA

control region could be increased during oncogenesis." (Page 682, column 2, lines 8-10.) Thus Alonso detected previously unknown mitochondrial mutations, not mtDNA mutations previously identified as somatic mutations in a tumor. Alonso teaches one mtDNA mutation that had previously been identified in tumor cells: "A 50 bp deletion in the mtDNA control region has also been described in gastric adenocarcinomas." (Page 682, column 2, lines 6-8.) This mutation, however, is not a single base pair mutation as recited in claim 35. Thus Alonso does not expressly or inherently teach "determining the presence of a single basepair mutation in a mitochondrial genome . . . wherein the mutation has previously been identified" as recited in claim 35.

The Rejection of Claims 2, 3, and 12-16 under 35 U.S.C. §§ 102(b) or 103(a)

Claims 2, 3, and 12-16 are rejected under 35 U.S.C. § 102 (b) as anticipated by or under 35 U.S.C. § 103(a) as obvious over Alonso. Claims 12-16 have been canceled, thus rendering their rejection moot. Applicants respectfully traverse the rejection as it applies to claims 2 and 3.

Claims 2 and 3 depend from claim 1. Claim 1 is directed to a method to aid in detecting the presence of tumor cells in a patient as discussed above. Claim 1 recites "determining the presence of a homoplasmic single basepair substitution." Claims 2 and 3 are dependent from claim 1 and thus contain this recitation.

To reject claims as *prima facie* obvious the Patent Office must satisfy three criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there

> must be a reasonable expectation of success. Finally, **the prior art reference (r references when c mbined) must teach r suggest all the claim limitations.**

MPEP § 2142; emphasis added. The rejection of amended claims 2 and 3 fails to meet the third criterion.

As discussed above, Alonso does not teach determination of "a homoplasmic single basepair substitution in a mitochondrial genome of a cell sample of a patient" as recited in claim 1. Alonso teaches mitochondrial mutations that were heteroplasmic transitions, heteroplasmic insertions, and homoplasmic deletions. (Page 684, column 2, line 6 to page 685, column 1, line 8.)

Alonso does not suggest identifying a tumor in a patient by detecting mutations in mtDNA. Although Alonso detected mutations in mtDNA, he does not suggest that these or any other mutations can be used to identify a tumor in a patient. Alonso teaches, "Further research is needed to address the significance of the mtDNA mutations observed in this study with regard to tumorigenesis." (Page 685, column 1, line 50 to column 2, line 2.) Thus Alonso does not suggest detecting any mtDNA mutation, including those he identified, to identify the presence of tumor cells. Alonso does not teach or suggest all the elements recited in claims 2 and 3 and therefore does not render claims 2 and 3 obvious.

Withdrawal of these rejections to claims 2, 3, and 12-16 is respectfully requested.

Alonso also does not render new claims 35-53 obvious. Claim 35 is the only independent claim of the new claim set. Claim 35, as discussed above, is directed to a method to aid in detecting the presence of tumor cells in a patient. The method recites

that a "single basepair mutation" is determined in a mitochondrial genome of the patient "wherein the mutation has previously been identified as a somatic mutation in a tumor."

As indicated above, Alonso does not teach this recitation of claim 35 because Alonso investigated if mtDNA mutations were present in tumor cells. "The aim of this study was to evaluate if this intrinsic [genetic] instability displayed by the mtDNA control region could be increased during oncogenesis." (Page 682, column 2, lines 8-10.)

Alonso also does not suggest this recitation of claim 35. Alonso does not suggest that single basepair mutations in mtDNA were known or that the mtDNA mutations he identified should be detected in a patient to identify a tumor. Alonso teaches that the significance of the mutations he identified with regard to tumorigenesis is unknown. (Page 685, column 1, line 50 to column 2, line 2.) Thus Alonso does not teach or suggest detecting the presence of a single basepair mitochondrial mutation "wherein the mutation has previously been identified as a somatic mutation in a tumor." Alonso does not teach or suggest all elements of claim 35.

The Rejection of Claims 4-8 and 30 under 35 U.S.C. § 103(a)

Claims 4-8 and 30 are rejected under 35 U.S.C. § 103(a) as obvious over Alonso in view of Sidransky (U.S. Patent No. 5,935,787; "the '787 patent") and Sidransky (U.S. Patent No. 6,025,127; "the '127 patent"). Applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1970). The combination of Alonso, the '787 patent, and the '127 patent fails to

teach or suggest all elements of claims 4-8 and 30. Thus the *prima facie* case of obviousness must fail.

Claims 4-8 and 30 depend from claim 1, which is directed to a method to aid in detecting the presence of tumor cells in a patient. In the method "a homoplasmic single basepair substitution in a mitochondrial genome of a cell sample of a patient" is determined. Alonso does not teach or suggest this step of claims 4-8 and 30 because Alonso teaches mtDNA mutations that include only heteroplasmic transitions, heteroplasmic insertions, or homoplasmic deletions. (Page 684, column 2, line 6 to page 685, column 1, line 8.) Alonso further teaches that it is unknown whether the mitochondrial mutations he identified are associated with tumors: "Further research is needed to address the significance of the mtDNA mutations observed in this study with regard to tumorigenesis." (Page 685, column 1, line 50 to column 2, line 2.) Thus Alonso also does not suggest that any mitochondrial mutation is used to identify a tumor in a patient.

The '787 patent does not remedy these defects of Alonso. The '787 patent teaches that hypermutable nucleic acid sequences can be used to detect cancers. (Column 5, lines 60-65.) The '787 patent teaches that hypermutable nucleic acid sequences are "preferably microsatellite DNA sequences which, by definition, are small tandem repeat DNA sequences." (Column 4, lines 14-16.) Thus, the '787 patent does not teach determining mutations in mtDNA or determining mutations in mtDNA that are homoplasmic single basepair substitutions.

The '127 patent also fails to remedy this defect of Alonso. The '127 patent teaches methods of detecting neoplastic nucleic acids in a tissue specimen external to the

primary tumor site. The neoplastic nucleic acids are detected in a sample of "DNA or RNA, including messenger RNA (mRNA), wherein DNA or RNA may be single stranded or double stranded." (Column 7, lines 15-17.) The '127 patent does not teach or suggest determination of mtDNA mutations or mtDNA mutations that are homoplasmic single basepair substitutions.

The combination of Alonso, the '787 patent, and the '127 patent fails to teach or suggest all the elements of amended claim 1. *A fortiori* it fails to teach or suggest all the elements of dependent claims 4-8 and 30. Therefore, the obviousness rejection must fail. Withdrawal of this rejection to claims 4-8, and 30 is respectfully requested.

New claims 35-53 are also not rendered obvious by this combination of references. As shown above, Alonso fails to teach or suggest all elements of independent claim 35 because Alonso does not teach or suggest that a single basepair mutation is determined in a mitochondrial genome of the patient "wherein the mutation has previously been identified as a somatic mutation in a tumor." The '787 patent and the '127 patent also do not teach or suggest this element. Thus the combination does not render claims 35-53 obvious.

The Rejection of Claim 11 under 35 U.S.C. § 103(a)

Claim 11 is rejected under 35 U.S.C. § 103(a) as obvious over Alonso in view of Chee *et al.* (*Science*, 1996, *274*, 610-613; "Chee"). Applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981

(CCPA 1970). The combination of Alonso and Chee fails to teach or suggest all elements of claim 11. Thus the *prima facie* case of obviousness against this claim must fail.

Claim 11 depends from claim 1, which is directed to a method to aid in detecting the presence of tumor cells in a patient. In the method, "a homoplasmic single basepair substitution in a mitochondrial genome of a cell sample of a patient" is determined. Alonso does not teach this recitation because Alonso teaches mtDNA mutations that include only heteroplasmic transitions, heteroplasmic insertions, or homoplasmic deletions. (Page 684, column 2, line 6 to page 685, column 1, line 8.)

Chee fails to remedy this defect of Alonso. Chee teaches an oligonucleotide array that contains probes complementary to the human mitochondrial genome. The arrays are used to detect polymorphisms in the mitochondrial genome and "three disease-causing mutations in a mtDNA sample from a patient with Leber's hereditary optic neuropathy." (Page 612, column 3, lines 7-9.) Chee does not teach that the oligonucleotide arrays are used to identify a human patient as having a tumor, much less that oligonucleotide arrays are used to detect a mtDNA mutation in a tumor wherein the mtDNA mutation is "a homoplasmic single basepair substitution." Thus the combination of Alonso and Chee fails to teach or suggest all elements recited in claim 11. The *prima facie* case of obviousness must fail. Withdrawal of this rejection to claim 11 is respectfully requested.

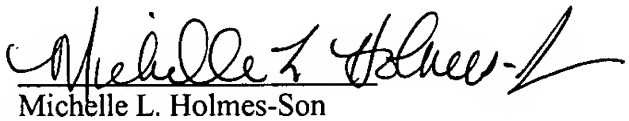
The rejection also should not apply to new claims 35-53 for the reasons discussed above.

The Rejection of Claims 1-16 and 29-32 for Obviousness-Type Double Patenting

Claims 1-16 and 29-32 have been rejected for obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,344,322. Claims 12-16 have been canceled thus rendering their rejection moot. A terminal disclaimer will be filed with respect to claims 1-11 and 29-32 upon receiving a notice of their allowability. Abeyance of this rejection is respectfully requested.

Respectfully submitted,

Date: February 6, 2003



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Appendix I. Marked Up Version of the Claims t Show the Changes Made

1. (Twice Amended) A method to aid in detecting the presence of tumor cells in a patient, comprising the steps of:

determining the presence of a homoplasmic single basepair [mutation] substitution in a mitochondrial genome of a cell sample of a patient, wherein the [mutation] substitution is found in a tumor of the patient but not in normal tissue of the patient; and

identifying the patient as having a tumor if one or more single basepair [mutations] substitutions are determined in the mitochondrial genome of the cell sample of the patient.

2. (Twice Amended) The method of claim 1 wherein, prior to the step of determining the presence of a single basepair substitution, the [mutation] substitution has been identified in a tumor.

29. (Amended) The method of claim 2 wherein the [mutation] substitution was identified previously in a tumor of the patient.

31. (Twice Amended) The method of claim 1 further comprising the step of testing a normal tissue of the patient to determine the absence of the [mutation] substitution in the normal tissue.